VALPROIC ACID ANALOGUES AND PHARMACEUTICAL COMPOSITIONS THEREOF

RELATED APPLICATIONS

[0001] This application claims priority from US Provisional Patent Application Serial No. 60/433,505 filed 16 December 2002.

TECHNICAL FIELD

[0002] This application relates to analogues of valproic acid, pharmaceutical compositions comprising the analogues, methods of synthesizing the analogues, and uses thereof.

BACKGROUND

[0003] Valproic acid (VPA) and the family of valproate salts are structurally simple drugs that possess a wide range of pharmacological activities. VPA compounds are among the few broad-spectrum anticonvulsants that are effective in both partial and generalized seizures. VPA and the related valproate salts are first line drugs of choice for epilepsy, bipolar disorder, and migraine prophylaxis.

[0004] However, despite the excellent efficacy profile of VPA and the related valproate salts, a variety of adverse effects limit their maximum dose and use. While VPA is a relatively safe drug in most patients, it is associated with a rare, frequently fatal, idiosyncratic liver toxicity, with the level of risk greatest in young children under 2 years of age and individuals on polytherapy. In addition, these drugs, like

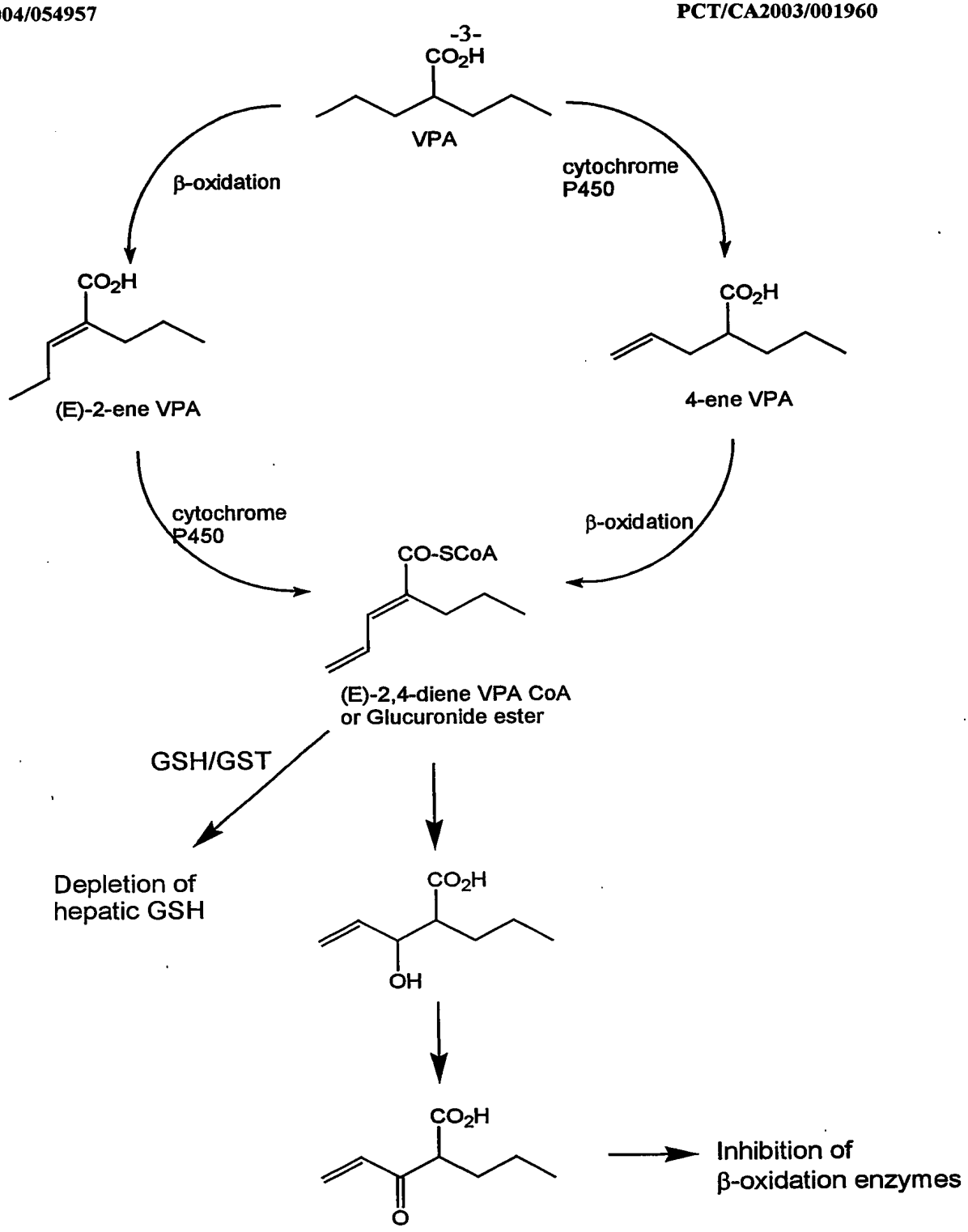
many other anticonvulsants, are also known teratogens and thus their use during pregnancy is limited.

VPA Associated Hepatotoxicity

[0005] The primary risk factors of fatal hepatotoxicity associated with VPA therapy are co-administration of other anti-epileptics known to induce cytochrome P450, such as phenytoin or phenobarbital, as well as administration to young age children (less than 2 years old).[1] As a result, reactive metabolites have been implicated in VPA-associated hepatotoxicity.

[0006] The VPA derivatives, 4-ene VPA (2-propylpent-4-enoic acid) and (E)-2,4-diene-VPA (2-propylpent-(E)-2,4-dienoic acid) have been demonstrated to induce massive lipid accumulation in rat liver. Expression of 4-ene VPA toxicity has been suggested to require further biotransformation via mitochondrial ß-oxidation to (E)-2,4-diene-VPA. The reaction of (E)-2,4-diene VPA, possibly in the CoA thioester form, with glutathione in mitochondria is postulated to produce a localized depletion of glutathione in susceptible individuals that would result in oxidative stress with accompanying hepatocellular damage.

[0007] Alternatively, (E)-2,4-diene-VPA may be eventually converted to 3-keto-4-ene VPA, a far more reactive species that inhibits certain ß-oxidation enzymes[2-4]. (E)-2,4-diene-VPA may also arise from the microsomal cytochrome P450 catalyzed dehydrogenation of the ß-oxidation metabolite (E)-2-ene VPA (2-propylpent-2-enoic acid), and the diene metabolite could react with hepatic glutathione through a glucuronide mediated pathway (Scheme 1).


-3-
CO2H
VPA
β-oxidation
cytochrome P450
CO2H
(E)-2-ene VPA
CO2H
4-ene VPA
cytochrome P450
β-oxidation
CO-SCoA
(E)-2,4-diene VPA CoA or Glucuronide ester
GSH/GST
Depletion of hepatic GSH
CO2H
OH
CO2H
O
Inhibition of β-oxidation enzymes

Scheme 1

VPA-Induced Teratogenicity

[0008] VPA causes neural tube defects leading to spina bifida in 1-2% of children born to mothers treated with VPA.[5] The risk appears to be related to the dose and peak levels of VPA as well as a history of neural tube defects. Metabolites do not appear to play a role. Structure-teratogenicity studies of VPA analogues indicate that in order to induce teratogenesis, the alpha carbon must be tetrahedral, must be connected to a free carboxylic acid group, and must be connected to one hydrogen atom and to two alkyl groups. Branching of the side chain alkyls reduces teratogenic potency as does the presence of a double bond at the 2-3 position. A double bond at the terminal position of the side chain of VPA maintains teratogenicity. Stereochemistry at the alpha carbon plays a role in the potency of teratogenic analogues.[6] The mechanism by which VPA produces birth defects is far from clear[7] and many mechanistic options have been proposed. VPA has been shown to produce reactive oxygen species (ROS) in vivo in the rat[8] and this can readily be reproduced in rat hepatocytes. The degree of ROS production is highly dependent on the plasma levels of VPA. Induction by phenobarbital and/or chronic administration of VPA to rats leads to significantly increased levels of VPA-induced ROS[8]. The ability of VPA to produce ROS has strong implications towards the mechanism of hepatotoxicity and also for teratogenic properties of this drug. Anticonvulsants, like phenytoin, that are teratogenic are also producers of ROS. The ability of a compound to generate ROS appears to be closely linked to the potential of that compound to cause embryotoxicity[9]. Hence, measurement of the ability of a VPA analogue

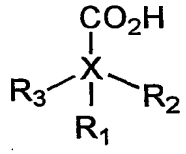
to produce ROS may be a strong indicator of the teratogenic potential of that compound.

[0009] Therefore, there is a need for effective, broad-spectrum anticonvulsants which have reduced or no hepatoxic and teratogenic side effects.

SUMMARY OF INVENTION

[0010] This application discloses analogues of valproic acid and methods of synthesizing and using same. The analogues are useful in the treatment or prophylaxis of conditions responsive to valproic acid therapy, including neuroaffective disorders such as convulsions, epilepsy, bipolar disorder, and migraine headaches.

[0011] The analogues comprise compounds represented by the formula (I) and stereoisomers and pharmaceutically acceptable salts thereof.



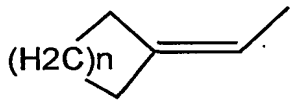
(I)

Preferably the analogues comprise between 5 and 13 carbon atoms, wherein X= C and wherein R_1 is optionally present and when present is either H or F.

[0012] When R_1 is present, R_2 and R_3 are selected from the group

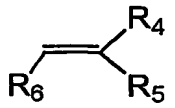
consisting of a linear or branched C1 to C6 alkyl, a linear or branched C2 to C6 n-ene hydrocarbyl (where n = 1 – 5), a linear or branched C1 to C6 n-yne hydrocarbyl (where n = 1 – 5), a linear or branched C1 to C5 ether, a linear or branched C1 to C6 ketone, and $-CH_x-A$ where A = cyclic C3 to C8 hydrocarbyl and x = 0 – 3. When R_1 is H, at least one of R_2 and R_3 are selectively fluorinated and when R_1 is F, R_2 and R_3 comprise linear or branched alkenyl groups.

[0013] In one embodiment when R_1 is not present, R_2 may be H, and there is a double bond between R_3 and X. In this embodiment R_3 is

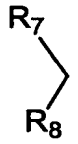


wherein n is 1 to 10.

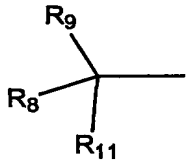
[0014] Alternatively, when R_1 is not present, there is a single bond between X and R_2, and R_2 is



wherein R_4, R_5, and R_6 are selected from the group consisting of H, methyl, ethyl, F, NH_2, cyclopropyl, CF_3, and saturated or unsaturated cyclic (C3 to C8) hydrocarbyl. In this alternative there is a double bond between R_3 and X, and R_3 is



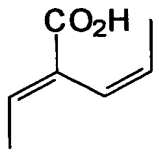
or



wherein R_7 and R_8 are selected from the group consisting of H, methyl, ethyl, F, NH_2, cyclopropyl and CF_3, and R_9, R_{10}, and R_{11} are selected from the group consisting of H, methyl, ethyl, F, NH_2, cyclopropyl and CF_3.

[0015] Preferably the analogue compounds have between 6 and 10 carbon atoms and may have 8 carbon atoms in one embodiment. The compounds may have multiple sites of alkene or alkyne unsaturation. In one embodiment the compounds may be selectively fluorinated at one or more secondary carbon atoms.

[0016] In one embodiment the analogue compounds are dienes having a E, Z configuration. For example, in one embodiment where R_1 is absent and R_2 and R_3 are unsaturated groups, the compounds may have a backbone having the following formula



wherein the backbone is optionally substituted by H, F, Me, Et, NH_2, or C1 to C3 hydrocarbyl groups.

[0017] This application discloses pharmaceutical compositions containing the valproic acid analogues and their pharmaceutically acceptable salts and prodrugs which are transformable into the valproic acid analogues and salts thereof.

[0018] Methods of making the valproic acid analogues and methods of treating neuroaffective disorders using the valproic acid analogues are also disclosed.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a concentration time curve of (E,Z)-2,3'-diene VPA levels in rat serum, liver and brain.

DESCRIPTION

[0019] Throughout the following description specific details are set forth in order to provide a more thorough understanding of the invention. However, the invention may be practiced without these particulars. In other instances, well known elements have not been shown or described in detail to avoid unnecessarily obscuring the

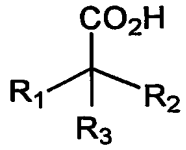
present invention. Accordingly, the specification and drawings are to be regarded in an illustrative, rather than a restrictive, sense.

[0020] This application describes novel analogues of VPA. The compounds are useful in the treatment or prophylaxis of neuroaffective disorders responsive to VPA therapy such as convulsions, epilepsy, bipolar disorder and migraine headaches. The compounds likely exhibit reduced or no hepatotoxic and/or teratogenic side effects compared to VPA. In one embodiment of the invention, the analogues either prevent or reduce the possibility of natural enzymatic processes reducing the carbon backbone at either the 2, 3 (or 2',3') or 3,4 (or 3',4') positions of the compounds. This is achieved through fluorination of the VPA analogues. Blocking the breakage of the carbon backbone results in reduction or elimination of metabolites implicated in the hepatoxicity of VPA. In a second embodiment, the analogues are cyclic VPA analogues. In a third embodiment, the analogues are conjugated analogues with stereodefined double bonds. In a fourth embodiment, the analogues are provided as pharmaceutically acceptable salts or pro-drugs. Methods of making the valproic acid analogues and using them in the treatment or prophylaxis of epilepsy, convulsions, bipolar disorders, migraine headaches, and other neuroaffective disorders are also described herein.

I) Fluorinated VPA Analogues

[0021] In a first embodiment of the invention, the compounds are selectively fluorinated analogues of VPA and derivatives thereof. For clarity, the following base, non-fluorinated, structures of VPA

analogues to which this embodiment of the invention can be applied are defined by the following base carboxylic acid structure:



Where:

Substituent	Possible	Preferred	Further Preferred
R_1	H, F, Cl, C1 to C3 Alkyl, or nothing (in the case of an unsaturated derivative).	H, F, Me	H
R_2	Linear or branched C1 to C6 alkyl; linear or branched C2 to C6 n-ene hydrocarbyl (where n = 1 – 5); linear or branched C1 to C5 ether; $-CH_x$-A where A = cyclic C3 to C8 hydrocarbyl and x = 0 – 3; linear or branched C1 to C6 n-yne hydrocarbyl (where n = 1 – 5); Linear or branched C1 to C6 ketones	Linear C2 to C4 alkyl; linear C2 to C4 n-ene hydrocarbyl (where n = 1 – 5); linear C1 to C5 ether; $-CH_x$-A where A = cyclic C3 to C8 hydrocarbyl and x = 0 – 1; linear C1 to C6 n-yne hydrocarbyl (where n = 1 – 5)	Propyl, propenyl, propynyl
R_3	Linear or branched C1 to C6 alkyl; linear or branched C2 to C6 n-ene hydrocarbyl (where n = 1 – 5); linear or branched C1 to C5 ether; $-CH_x$-A where A = cyclic C3 to C8 hydrocarbyl and x = 0 – 3; linear or branched C1 to C6 n-yne hydrocarbyl (where n = 1 – 5); Linear or branched C1 to C6 ketones	Linear C2 to C4 alkyl; linear C2 to C4 n-ene hydrocarbyl (where n = 1 – 5); linear C1 to C5 ether; $-CH_x$-A where A = cyclic C3 to C8 hydrocarbyl and x = 0 – 1; linear C1 to C6 n-yne hydrocarbyl (where n = 1 – 5)	Propyl, propenyl, propynyl

Table 1: VPA Analogue Constituent Structures

[0022] The total number of carbon atoms in the molecule is between 5 and 13. In embodiments of the invention, the total number of

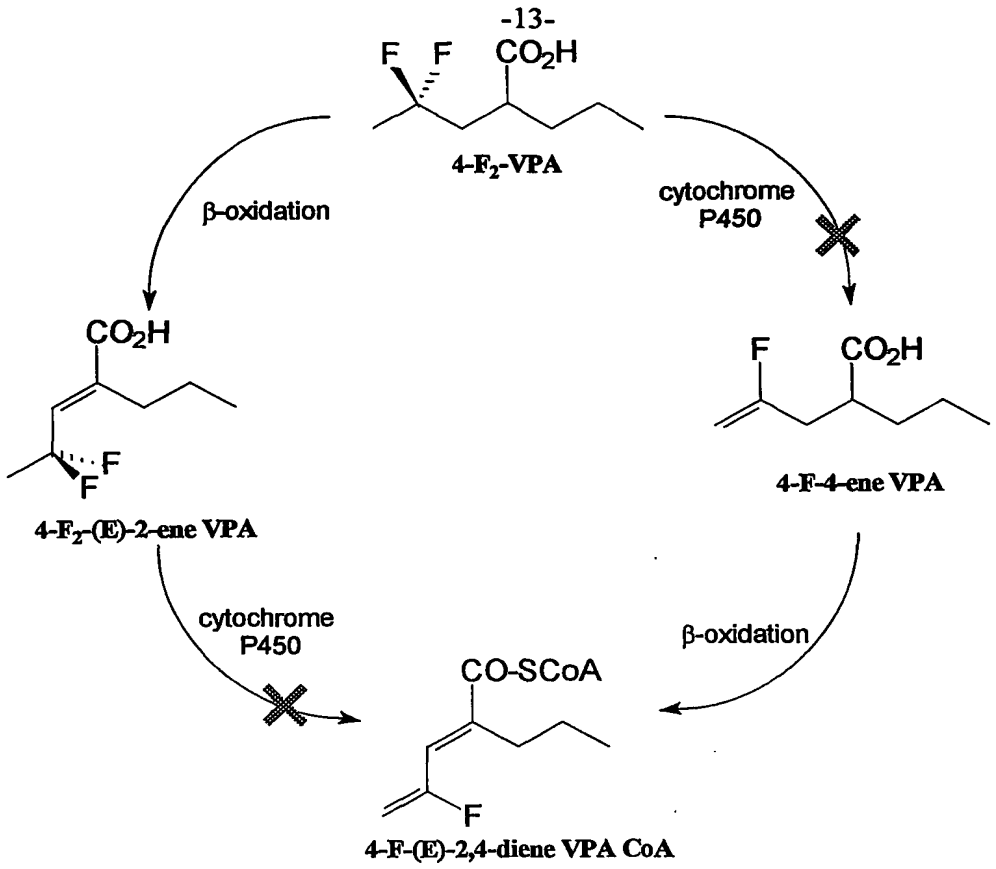
carbon atoms in the molecule is between 6 and 10, and in one embodiment the total number of carbon atoms in the molecule is eight.

[0023] The compounds of this embodiment of invention are VPA analogues as described in Table 1 above in which one or more of the primary, secondary or tertiary carbon atoms have been halogenated. In a preferred embodiment the halogen used is fluorine and the carbon atom(s) is/are secondary carbon atom(s). The halogenated carbon atom may be of sp^2 or sp^3 hybridization.

[0024] Preferably, the halogen in use is fluorine, due to the strength of the carbon-fluorine bond verses the strength of other carbon-halogen bonds. However, the use of other halogens is also contemplated by this invention.

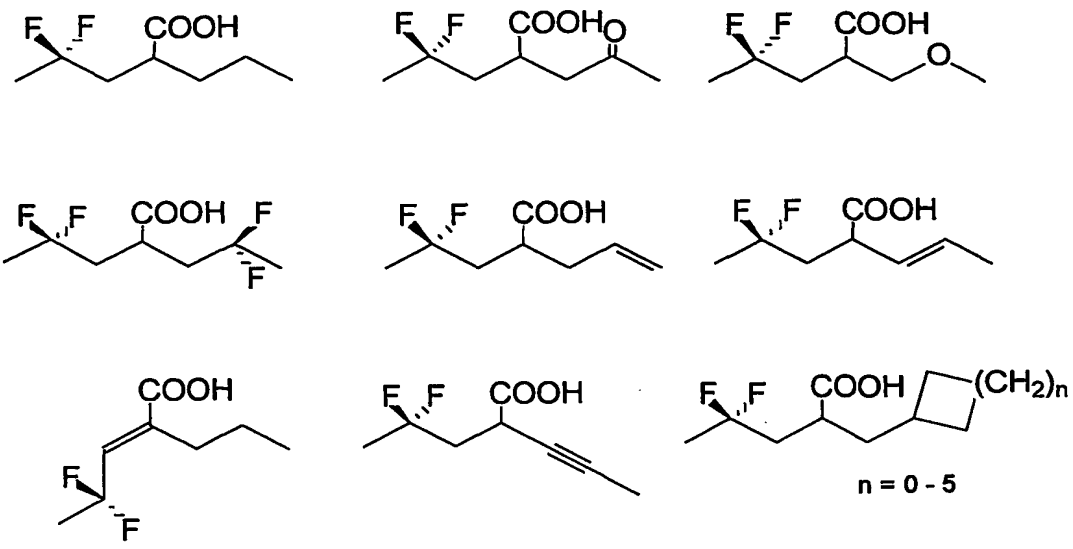
A) Prevention of 4-ene metabolite formation:

[0025] The compounds of the first embodiment include compounds that are selectively fluorinated at the 4 and/or 4' position of the carbon backbone so as to prevent the formation of a double bond between the 4 and 5 (or 4' and 5') carbon. An example is shown in Scheme 2 where the 4 position is fully fluorinated (4-F_2-VPA). As depicted in Scheme 2, cytochrome P450 (or other enzymes of related function) is unable to cleave the carbon-fluorine bond to form a terminal CH_2=CF- moiety. The formation of a glucuronide analogue along these metabolic pathways is therefore disrupted and the hepatotoxic potential of the VPA analogue is reduced.

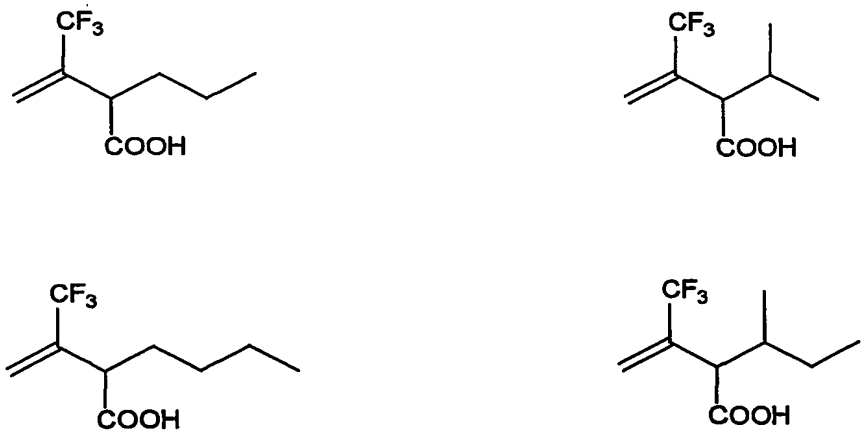


Scheme 2

[0026] Possible compounds of this embodiment include, but are not limited to:

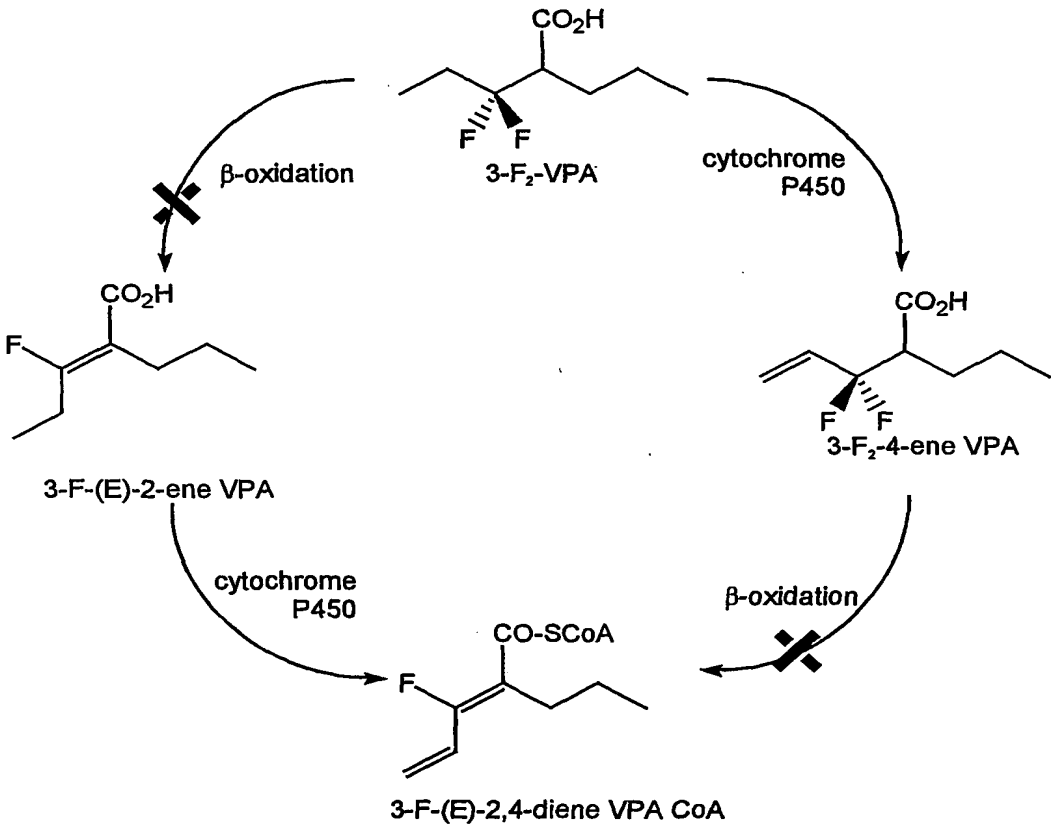


[0027] The compounds of the first embodiment also include compounds fluorinated at the terminal (primary) carbon of a propyl/propenyl/propynl carbon chain attached to the carbon at position 2 or 2'. Fluorination in the 5 and/or 5' position(s) will have a similar effect as fluorination at the 4 and/or 4'-position in preventing 4 (and/or 4')-ene formation. In preferred embodiments, fluorination at the 5' position is present in moieties that are at least C4 chains, such that the fluorination occurs at a secondary carbon atom. Compounds contemplated by this embodiment include:



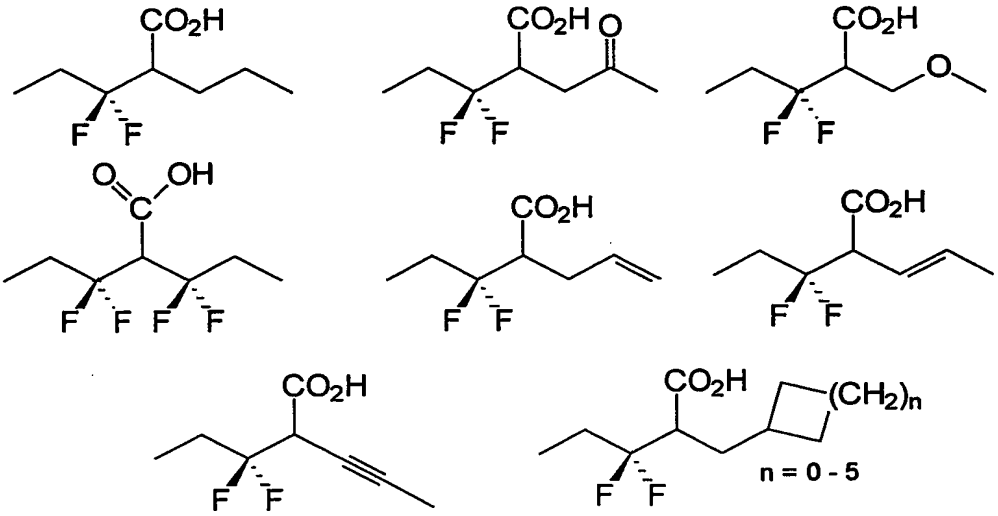
B) Prevention of 2-ene metabolite formation

[0028] The compounds of the first embodiment also include VPA analogues that are fluorinated at the 3 and/or 3' secondary carbon atoms. As depicted in Scheme 3 below, the formation of a glucuronide analogue along these metabolic pathways is disrupted and the hepatotoxic potential of the VPA analogue is therefore reduced.

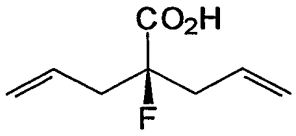


Scheme 3

[0029] Possible compounds of this embodiment include, but are not limited to:

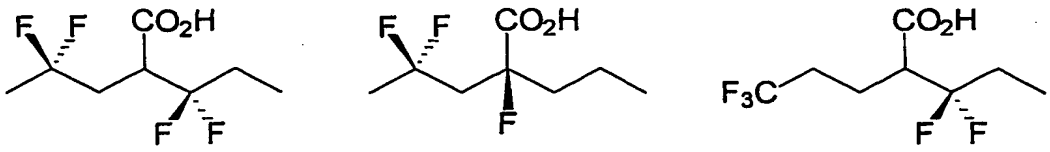


[0030] The following analogue and similar compounds that are α-fluorinated are also contemplated by the invention.

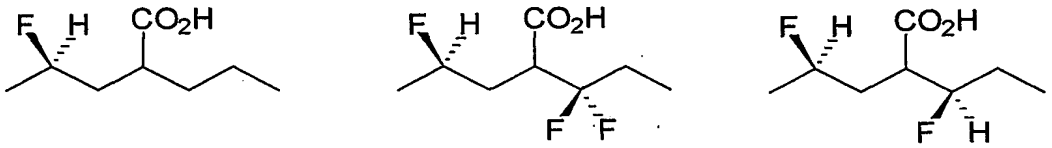


In this embodiment R_2 and R_3 may comprise linear or branched alkenyl groups.

[0031] Compounds that are selectively fluorinated at a number of different secondary carbon atom positions are also contemplated within the scope of this invention. Primary and/or tertiary carbon atoms may also be optionally functionalised with fluorine atoms within the same structure. Possible compounds of this embodiment include, but are not limited to:



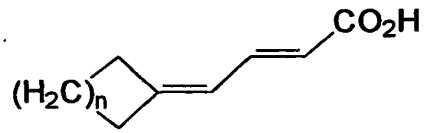
[0032] This invention also contemplates compounds with mono-fluorinated secondary carbon atoms. These compounds take advantage of the high stereoselectivity of enzymatic processes. For instance, it is known that cytochrome P450 and other enzymes that carry out oxidation reactions can act with high stereospecificity when cleaving carbon-hydrogen bonds. Compounds that are monofluorinated at secondary carbon atoms may prevent the oxidation of the substrate by enzymes. Some examples of compounds that are contemplated within this embodiment are shown below. However, these compounds should not be considered as limiting the scope of the invention.



II) Cyclic VPA Analogues

[0033] In a second embodiment of the invention, the compounds comprise cyclic VPA analogues. These unsaturated analogues of 2-ene VPA were investigated based on the reported properties of the major metabolite, 2-ene VPA to be less hepatotoxic and embryotoxic than VPA. The results reported by Palaty and Abbott[13] show that cyclic analogues of 2-ene VPA were more potent than VPA, based on their respective concentrations in brains. Neurotoxicity was less or equivalent to that of VPA. The compounds described by the following

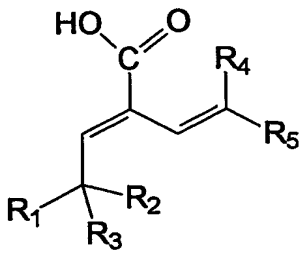
structure are also likely useful for treating individuals with epilepsy, or others in need of anticonvulsant therapy.

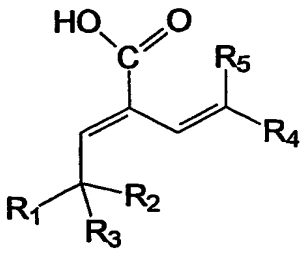


[0034] In these compounds n may be between 0 and 10, and is preferably between 4 and 8. In some embodiments, n is 4 or 5. The E isomer is shown above. However both the E and Z isomers are contemplated within the scope of these embodiments. Furthermore, any position on either the dialkenyl chain or the cyclic hydrocarbyl may be optionally functionalised with halogen (particularly F) or C1 to C3 hydrocarbyl group.

III) Conjugated VPA Analogues

[0035] In a third embodiment, the invention contemplates VPA analogues containing the (E)-1-(Z)-2'-diene VPA and (E)-1-(E)-2'-diene VPA backbones. These analogues are an extension of the 2-ene VPA analogues and likely have the same beneficial properties, i.e. potency like VPA with reduced liver toxicity and teratogenic properties. A unique finding was that the geometric isomer having the (E)-2-(Z)-3'-diene configuration had greater potency and less neurotoxic effects than the corresponding (E)-2-(E)-3'-diene isomer[13]. The carbon skeletons of these conjugated VPA analogues are shown below:





[0036] Without limitation, the following R substituents are possible embodiments of such conjugated analogues.

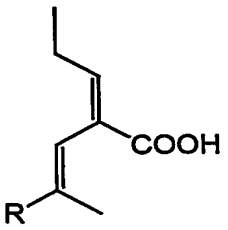
R_1 = H, Me, Et, Cyclopropyl, CF_3

R_2, R_3 = H, F

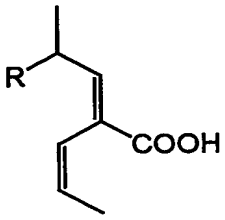
R_4 = H, Me, Et, F, CF_3, saturated or unsaturated cyclic (C3 to C8) hydrocarbyl

R_5 = H

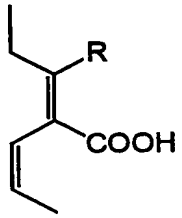
[0037] In another embodiment the invcntion also includes amine substituted conjugated VPA analogues. Some examples of compounds that are contemplated within this embodiment are shown below. However, these compounds should not be considered as limiting the scope of the invention.



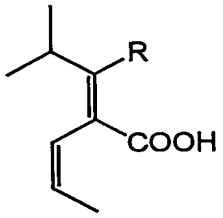
R = F, Me, NH_2



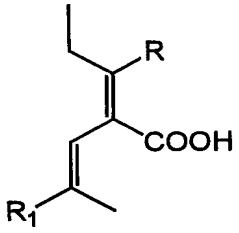
R = F, Me, NH_2



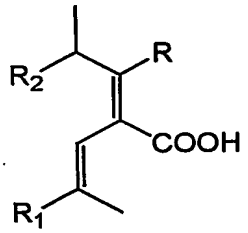
R = F, Me, NH_2



R = F, Me, NH_2



R = F, Me, NH_2
R_1 = F, Me, NH_2, H



R_1, R_2, R_3 = F, Me, NH_2, H

[0038] It will be apparent to those skilled in the art that all of the compounds of the invention described herein may exist in enantiomeric or diastereomeric forms, and that pure enantiomers or diastereomers may be resolved or separated from the racemate or mixture by methods well known in the art. Alternatively, enantiomeric or diastereomeric forms may be prepared by chiral synthesis. R and S enantiomers, racemates, non-racemic mixtures of enantiomers, and mixtures of diastereomers are all contemplated within the scope of this invention.

[0039] The VPA analogues described herein may be provided as pharmaceutically acceptable salts or prodrugs. Suitable salts include, but are not limited to, ammonium, sodium, potassium, calcium and

magnesium salts. Suitable prodrugs include, but are not limited to, alkyl esters, alkoxy-alkyl esters, hydroxyalkyl esters and amides.

[0040] The invention also relates to a method for treating individuals with epilepsy, or for treating others in need of anticonvulsant therapy. Mammals, and in particular humans, who would benefit from this method of treatment include those exhibiting, or at risk of exhibiting, any type of seizure activity. The method of the invention comprises administering to an individual a therapeutically effective amount of at least one compound described herein, or a salt or prodrug thereof, which is sufficient to reduce or prevent seizure activity.

[0041] The invention also relates to methods of treating or preventing other neuraffective disorders including bipolar disorder and migraine headaches. The method of the invention comprises administering to an individual a therapeutically effective amount of at least one compound described herein, or a salt or prodrug thereof, which is sufficient to reduce or prevent bipolar disorder, migraine headache, and other neuroaffective disorders.

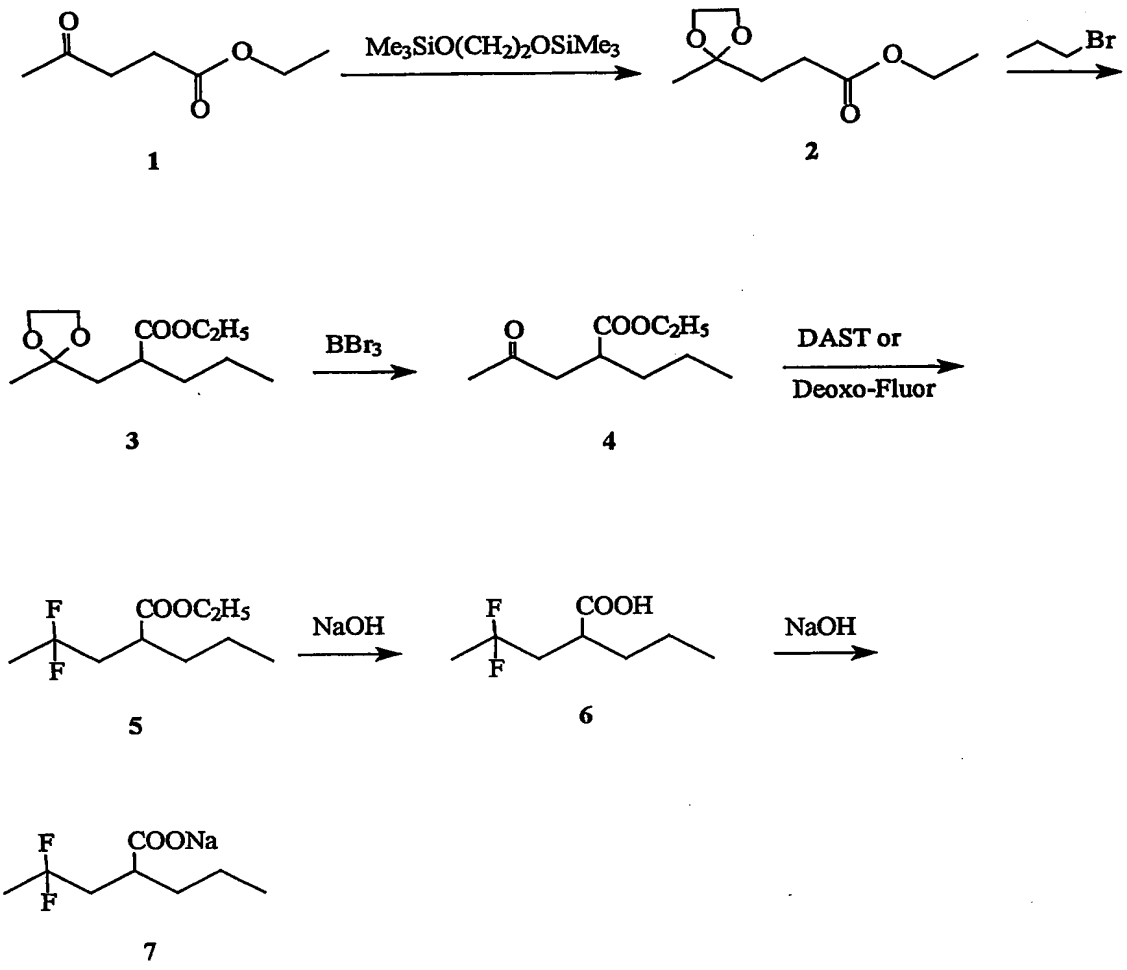
IV) Examples

[0042] The following are examples which are intended to illustrate the embodiments of the invention and which are not intended to limit the scope of the invention.

Example 1: Chemical Synthesis of Fluorinated VPA Analogues

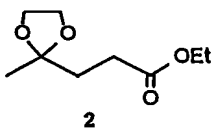
A) Preparation of sodium 4,4-difluoro-2-propylpentanoate (7)

[0043] The synthetic scheme shown in Scheme 4 below illustrates the synthesis of sodium 4,4-difluoro-2-propylpentanoate **7** and related analogues. The choice of the protecting group[23-27] is important to the success of the reaction sequence and the protection of the carbonyl group of **1** under a variety of conditions was investigated. When the acetalization of **1** was carried out using the silylated alcohol $Me_3SiO(CH_2)_2OSiMe_3$ and a catalytic amount of TMSOTf[27] at -78°C the cyclic acetal **2** was obtained in a quantitative yield. The *gem*-difluorination of keto ester **4** which is the crucial step of the reaction sequence was carried out under a number of reaction conditions.[28-32] Fluorination of **4** with DAST[33,34] or Deoxo-Fluor[30-32] gave the target ethyl 4,4-difluoro-2-propylpentanoate **5**. **Scheme 4** below describes ester hydrolysis and preparation of the sodium salts of the end compounds. An alternative approach to the synthesis of **4** is described in Scheme 5.[33-35]



Scheme 4

Preparation of ethyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate (2)

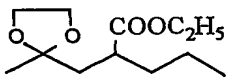


A pre-cooled mixture (-78°C) of TMSOTf (1.56 g) in CH_2Cl_2 (7 ml) was treated with 1,2-bis(triethylsilyloxy)ethane (16.33 g) and ethyl

levulinate (10.09 g) respectively under nitrogen, and the reaction mixture was stirred for 4.5 h. The reaction mixture was treated with pyridine, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by vacuum distillation to give 12.9 g of compound **2** as a colourless liquid having bp 63°C/0.3 mmHg.

^{1}H NMR (300 MHz, $CDCl_3$): 4.03 (q, 2H), 3.84 (m, 4H), 2.29 (t, 2H), 1.92 (t, 2H), 1.23 (s, 3H), 1.16 (t, 3H).

Preparation of ethyl-2[(2-methyl-1,3-dioxolon-2-yl)methylpentanoate (3).



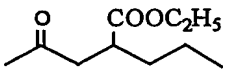
3

A solution of LDA (7.88 g) in THF (45 ml) was treated with HMPA (12.81 ml) at -78°C. After 30 min a solution of 11.8 g of compound **2** in THF (15 ml) was added for 60 min and stirred for 60 min. Propyl bromide (8.1 ml) in THF (10 ml) was added for 30 min, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with sat. NH_4Cl (150 ml), the organic layer was separated and the water phase was extracted with ethyl acetate. The combined organic extracts were washed with brine

and dried over magnesium sulfate. After distilling off the solvent, compound **3** was obtained in 83% yield, bp 82-83°C/2 mmHg.

^{1}H NMR (300 MHz, $CDCl_3$): 3.97 (q, 2H), 3.75 (m, 4H), 2.39 (m, 1H), 2.06 (dd, 1H), 1.54 (dd, 1H), 1.44-1.14 (m, 7H), 1.10 (t, 3H), 0.74 (t, 3H).

Preparation of ethyl 4-oxo-2-propylpentanoate (4)



4

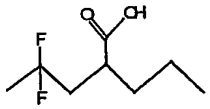
Method 1(Scheme 4): 9.2 g of compound **3** in hexane (300 ml) were cooled to -60°C and boron tribromide (1.0 M solution, 60 ml) was added dropwise and the reaction mixture was warmed to -10°C. After stirring for 2 hours it was treated with H_2O (150 ml), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate = 10:1) to give compound **4** in 87% yield.

Method 2 (Scheme 5): A mixture of cuprous chloride (3.96 g) and palladium(II) chloride (1.4 g) in N,N-dimethylformamide (40 ml) and water (40 ml) was vigorously shaken under oxygen atmosphere until the absorption of oxygen ceased. Compound **22** (6.81 g) (Scheme 5) was added and the reaction mixture was shaken at room temperature for 24 hours. The reaction mixture was poured into 10%HCl (150 ml) and

extracted with methylene chloride, dried over magnesium sulfate and concentrated under reduced pressure. After fractionating, a clear colourless liquid of compound **4** was obtained in 65% yield, bp 75-76°C/2 mmHg.

^{1}H NMR (300 MHz. $CDCl_3$): 4.01 (q, 2H), 2.75 (m, 2H), 2.38 (m, 1H), 2.04 (s, 3H), 1.51-1.26 (m, 4H), 1.13 (t, 3H), 0.79 (t, 3H).

Preparation of 4,4-difluoro-2-propylpentanoic acid (6).



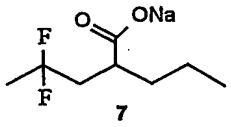
6

A solution of 2.2 g of compound **4** in methylene chloride (15 ml) was treated with Deoxo-Fluor (3.96 g) and the reaction mixture was stirred at 60°C for 48 hours. The reaction mixture was cooled to 0°C and treated with sat. $NaHCO_3$ until effervescence was completed. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate. The solvent was distilled off and the residue was separated from the unreacted compound **4** by column on silica gel (hexanes:ethyl acetate= 20/1). The residue obtained was refluxed with 2.2 N NaOH (25 ml) for 1.5 h. After cooling to 0°C the reaction mixture was treated with 10% HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure. The residue was

purified by column on silica gel (hexanes:ethyl= acetate 5:1) to give 460 mg of compound **6**.

^{1}H NMR (300 MHz. $CDCl_3$): 11.55 (br s, 1H), 2.73-2.63 (m, 1H), 2.39 (m, 1H), 1.99 (m,1H), 1.94-1.82 (m, 7H), 0.91 (t, 3H).

Preparation of sodium 4,4-difluoro-2-propylpentanoate (7)



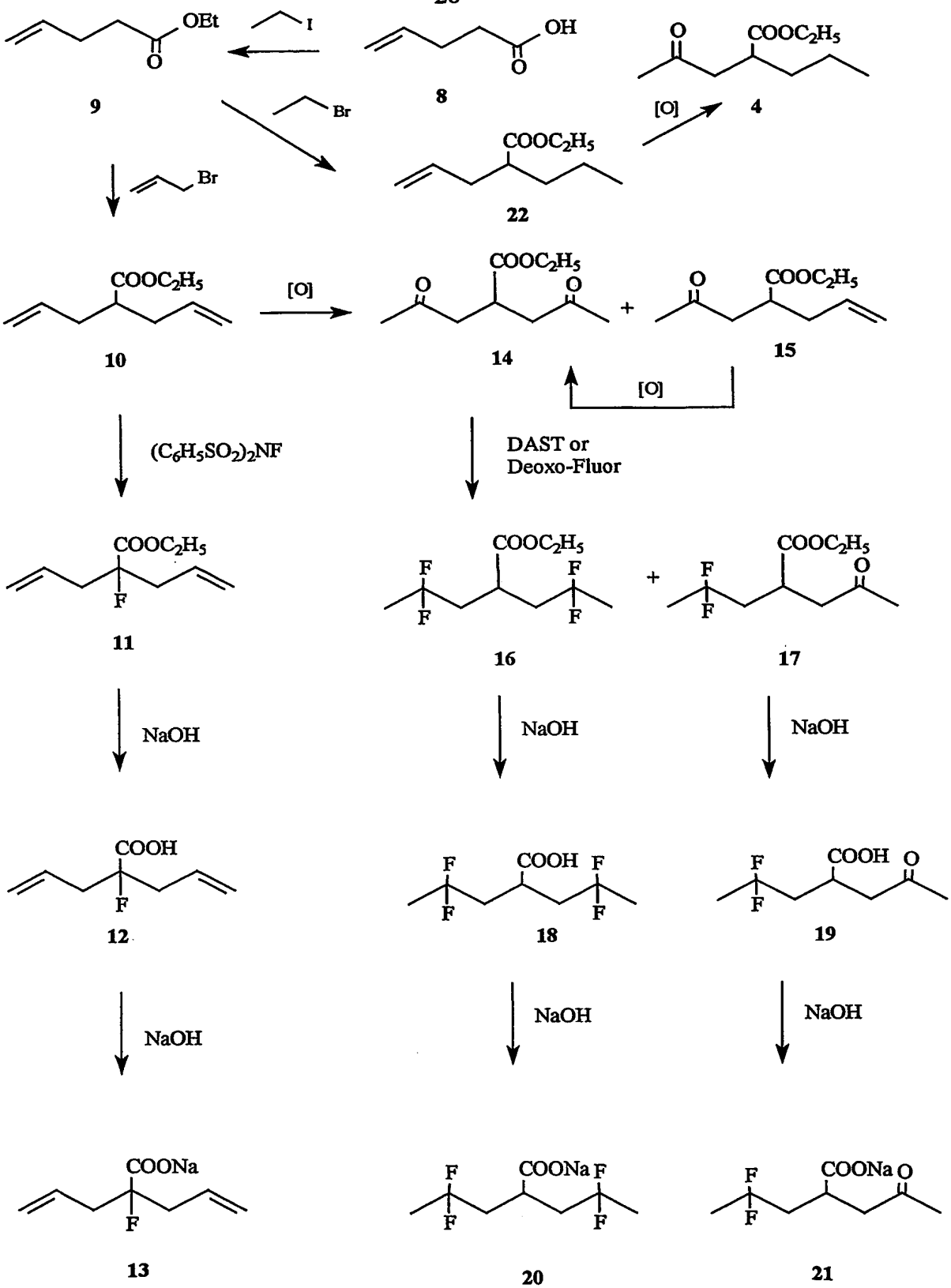
7

To a solution of 373 mg of compound **6** in methanol (5 ml), 80 mg of sodium hydroxide in methanol (25 ml) was added. The reaction mixture was stirred overnight and the methanol was evaporated under reduced pressure. The residue was washed with ethyl acetate and petroleum ether, successively to give 345 mg of compound 7 as a white powder.

^{1}H NMR (300 MHz. $CDCl_3$): 2.33 (m, 2H), 1.81 (t, 1H), 1.57 (t, 3H), 1.55 (m, 1H), 1.47 (m, 3H), 0.91 (t, 3H).

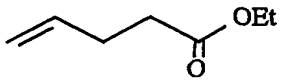
B) Synthesis of sodium 2-allyl-2-fluoropent-4-enoate (13).

[0044] The preparation of target compound **12** and its sodium salt **13** was achieved by fluorination of the precursor **10** with $(PhSO_2)_2NF$[10] in the presence of LDA in THF at -78°C to give ester **11** in 39% yield **(Scheme 5)**.


OEt
I
OH
O
COOC2H5
9
8
4
[O]
Br
22
10
14
15
(C6H5SO2)2NF
DAST or
Deoxo-Fluor
11
16
17
NaOH
12
18
19
13
20
21
COOH
COONa
F

Scheme 5

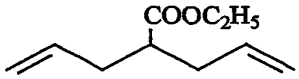
Preparation of ethyl pent-4-enoate (9)



9

A mixture of 4-pentenoic acid (10.01 g), ethyl iodide (31.19 g), potassium carbonate (10.36 g) and 18-crown-6 (1.28 g) in dry THF (100 ml) was refluxed for 6 hours. After cooling the white solid formed was filtered, and the filtrate was fractionated under reduced pressure to give compound **9** in 80% as a colourless oil, bp 43-44°C/12 mmHg.

Preparation of ethyl 2-allylpent-4-enoate (10)

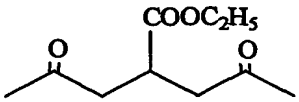


10

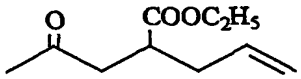
To a pre-cooled at -78°C solution of LDA (10 g) prepared from diisipropylamine and BuLi (1.6 M in hexane) in tetrahydrofuran (58 ml) was added dropwise HMPA (16.3 ml). After 15 minutes, 10.21 g of compound **9** in THF (10 ml) was slowly added. After 60 minutes, allyl bromide (13.69 g) in THF (10 ml) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with saturated ammonium chloride, extracted with ether, washed with brine, and dried over magnesium sulfate. The mixture was filtered and the solvent distilled off. The residue was purified by

vacuum distillation to afford compound **10** in 63% yield as a colourless oil, bp 36-38°C/0.5 mmHg.

Preparation of ethyl 4-oxo-2-(2-oxopropyl)pentanoate (14) and ethyl 2-(2-oxopropyl)pent-4-enoate (15).



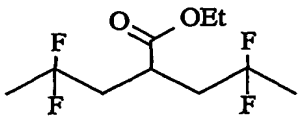
14



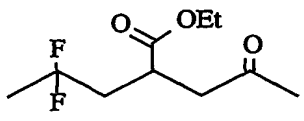
15

A mixture of cuprous chloride (5.13 g) and palladium(II) chloride (800 mg) in N,N-dimethylformamide (46 ml) and water (3.2 ml) was vigorously shaken under oxygen atmosphere until the absorption of oxygen ceased. 4.41 g of compound **18** was added and the reaction mixture was shaken at room temperature for 24 hours. The reaction mixture was poured into 10% HCl and extracted with methylene chloride, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate= 10:1) to give compounds **14** and **15** in 24% and 60% yield, respectively as colourless oils.

Preparation of ethyl 2-(2,2-difluoropropyl)-4,4-difluoropentanoate (16) and ethyl 4,4-difluoro-2-(2-oxopropyl)pentanoate (17)



16



17

A mixture of 3 g of compound **15** in dry CH_2Cl_2 (15 ml) was treated dropwise with DAST (8 ml) at 0°C and the reaction mixture was stirred at room temperature for 96 hours. The mixture was then poured into ice-water and the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate= 15:1) to give 367 mg and 864 mg of compounds **16** and **17**, respectively as a white solids.

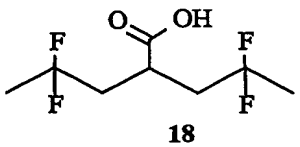
Compound **16**:

^{1}H NMR (300 MHz, $CDCl_3$): 4.14 (q, 2H), 2.92 (m, 1H), 2.41-2.22 (m, 2H), 2.08-1.89 (m, 2H), 1.59 (t, 6H), 1.22 (t, 3H).

Compound **17**:

^{1}H NMR (300 MHz, $CDCl_3$): 4.06 (q, 2H), 3.04-2.96 (m, 1H), 2.89-2.81 (m, 1H), 2.69-2.62 (m, 1H), 2.33-2.25 (m, 1H), 2.21 (s, 3H), 2.04-1.88 (m, 1H), 1.54 (t, 3H), 1.16 (t, 3H).

Preparation of 2-(2,2-difluoropropyl)-4,4-difluoropentanoic acid (18)



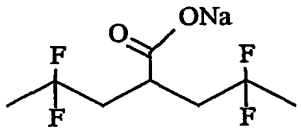
18

A solution of 157 mg of compound **16** was refluxed with 2.2 N NaOH (25 ml) for 1.5 hours. After cooling to 0°C the reaction mixture

was treated with 10% HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexanes:ethyl=acetate 5:1) to give 120 mg of compound **18**.

^{1}H NMR (300 MHz. $CDCl_3$): 11.35 (br s, 1H), 3.04-2.99 (m, 1H), 2.45-2.27 (m, 2H), 2.11-2.05 (m, 2H), 1.62 (t, 6H).

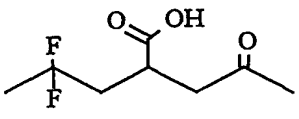
Preparation of sodium 2-(2,2-difluoropropyl)-4,4-difluoropentanoate (20)



20

To a solution of 329 mg of compound **18** in methanol (5 ml), 58 mg of sodium hydroxide in methanol (20 ml) was added. The reaction mixture was stirred overnight and the methanol was evaporated under reduced pressure. The residue was washed with ethyl acetate and petroleum ether, successively, to give 323 mg of compound **20** as a white powder.

Preparation of 4,4-difluoro-2-(2-oxopropyl)pentanoic acid (19)

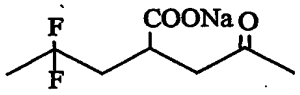


19

A solution of 805 mg of compound **17** was refluxed with 2.2 N NaOH (25 ml) for 1.5 hours. After cooling to 0°C the reaction mixture

was treated with 10% HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexanes:ethyl= acetate 3:1) to give 371 mg of compound **19**.

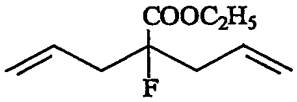
Preparation of sodium 4,4-difluoro-2-(2-oxopropyl)pentanoate (21)



21

To a solution of 303 mg of compound **19** in methanol (5 ml), 60 mg of sodium hydroxide in methanol (30 ml) was added. The reaction mixture was stirred overnight and the methanol was evaporated under reduced pressure. The residue was washed with ethyl acetate and petroleum ether, successively, to give 300 mg of compound **21** as a white powder.

Preparation of ethyl 2-allyl-2-fluoropent-4-enoate (11)

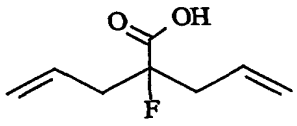


11

To a pre-cooled (at -78°C) solution of LDA (2.37 g) in tetrahydrofuran (30 ml) was added dropwise HMPA (3.85 ml). After stirring for 15 min a solution of 2.6 g of compound **10** in tetrahydrofuran (10 ml) was added over 1.5 h and stirred for 30

minutes. A solution of N-fluorobenzene sulfonimide (8.2 g) in tetrahydrofuran (30 ml) was then added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with saturated ammonium chloride and 10% HCl, respectively. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, and dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate= 30:1 to 20:1) to give 1.1 g of compound **11**.

Preparation of 2-Allyl-2-fluoropent-4-enoic acid (12)

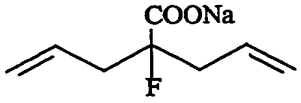


12

A mixture of 1.1 g of compound **11** and 2.2 N sodium hydroxide (35 ml) was heated at 60°C for 96 hours. The reaction mixture was cooled to 0°C and treated with 10% HCl until pH 1 was attained. The mixture was then extracted with ethyl acetate, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate= 10:1) to give 592 mg of compound **12**.

^{1}H NMR (300 MHz. CD_3OD): 5.79 (m, 2H), 5.16 (d, 4H), 2.64 (d, 2H), 2.55 (d, 2H).

Preparation of sodium 2-allyl-2-fluoropent-4-enoate (13)

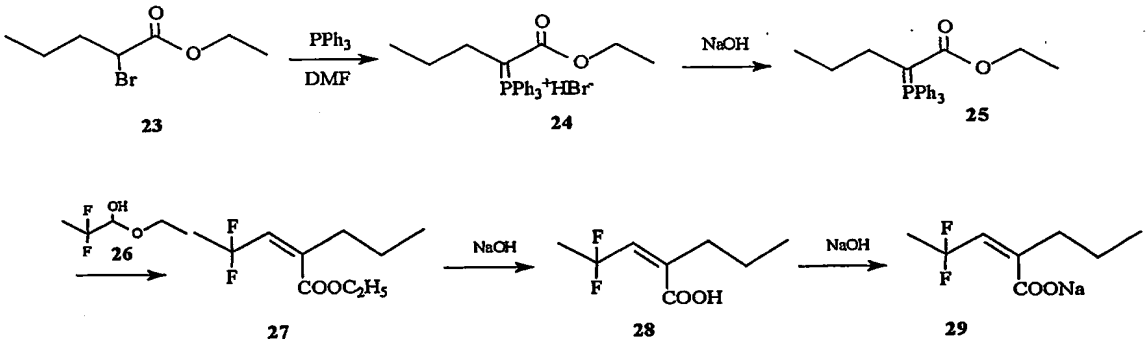


13

A mixture of 818 mg of compound **12** in methanol and 195 mg of sodium hydroxide in methanol (55 ml) was stirred overnight and the methanol was evaporated under reduced pressure. The residue was washed with ethyl acetate and petroleum ether, successively, to give 859 mg of compound **13** as a white solid.

^{1}H NMR (300 MHz. CD_3OD): 5.84 (m, 2H), 5.09 (td, 4H), 2.71-2.41 (m, 4H).

C) Synthesis of sodium (2Z)-4,4-difluoro-2-propylpent-2-enoate (29)

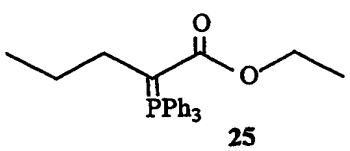


23 **24** **25**

27 **28** **29**

Scheme 6

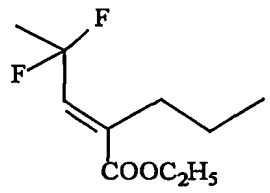
Preparation of ethyl 2-(triphenylphosphoranylidene)pentanoate (25)



25

Compound **25** was prepared according to the procedure described in US Patent 4,965,401 (1990).

Preparation of ethyl (2E)-4,4-difluoro-2-propylpent-2-enoate (27)

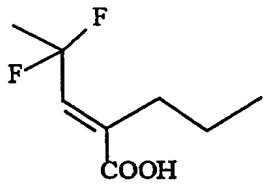


27

A mixture of 510 mg of compound **25**, pTSA (19 mg) and ethyl 2,2-difluoropropanoate 25[48] in methylene chloride (12 ml) was refluxed for 24 hours. The solid formed was filtered and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate=15:1) to give 810 g of compound **27**.

^{1}H NMR (300 MHz. $CDCl_3$): 6.60 (t, 1H), 4.21 (q, 2H), 2.41 (t, 2H), 1.74 (t, 3H), 1.45 (dq, 2H), 1.29 (t, 3H), 0.92 (t, 3H).

Preparation of (2*Z*)-4,4-difluoro-2-propylpent-2-enoic acid (28)

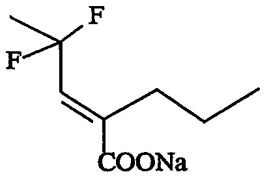


28

A mixture of 252 mg of compound **27** and 2.2 N sodium hydroxide (3 ml) was heated at 60°C for 2 hours. The reaction mixture was concentrated under reduced pressure and treated with 1N HCl. The mixture was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column on silica gel (hexane:ethyl acetate=10:1) to give 198 mg of compound **28**.

^{1}H NMR (300 MHz, $CDCl_3$): 12.17 (br s, 1H), 6.76 (t, 1H), 2.42 (t, 2H), 1.75 (t, 3H), 1.49 (dq, 2H), 0.94 (t, 3H).

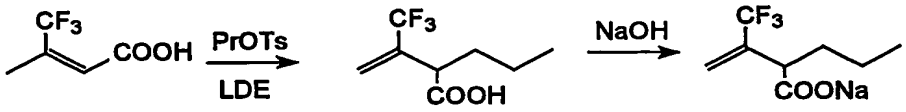
Preparation of sodium (2Z)-4,4-difluoro-2-propylpent-2-enoate (29)



29

Compound **29** was prepared according to the procedure described above for the preparation of sodium 4,4-difluoro-2-propylpentanoate (compound **7**).

D) Synthesis of sodium 2-propyl-3-(trifluoromethyl)but-3-enoate (32).



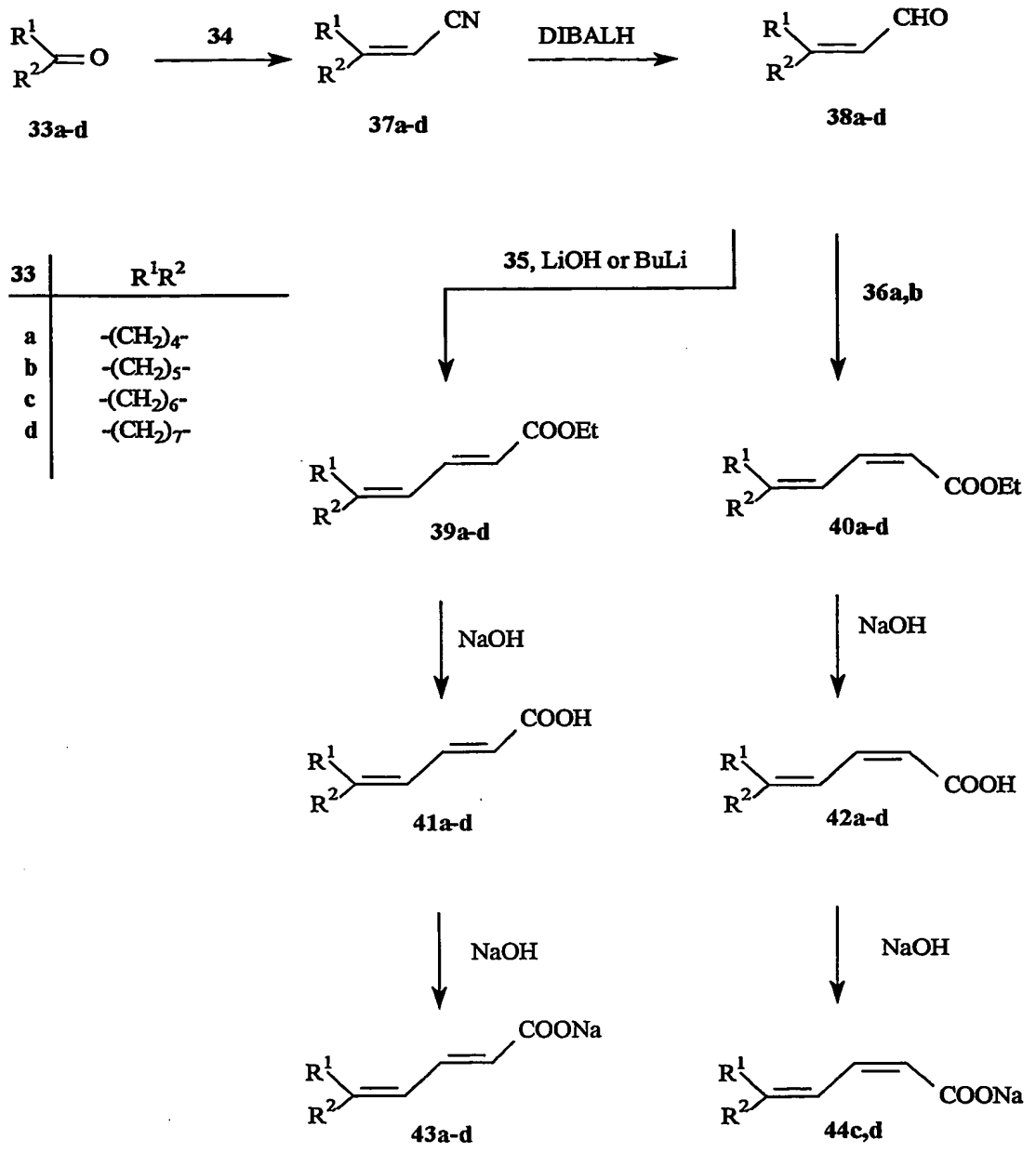
30 31 32

Scheme 7

[0045] The preparation of 2-propyl-3-(trifluoromethyl)but-3-enoic acid **31** and its sodium salt **32** outlined in Scheme 7 above illustrates the approach to the synthesis of VPA analogues containing a CF_3-group.[36-38]

Example 2: Synthesis of Cyclic VPA Analogues

[0046] The Wittig reaction and its modification, the base-promoted Horner-Wadsworth-Emmons olefination of aldehydes and ketones with phosphonate carbanions, is a widely employed approach to the synthesis of α,β- unsaturated esters[41]. In order to synthesize selected substituted (2*E*)- and (2*Z*)-4-substituted but-2-enoic acids, the inventors' strategy was based on the coupling of the β,β-disubstituted α,β-unsaturated aldehydes **38** and the generated phosphonate carbanions under specific conditions that provide high E- and Z-stereoselectivity (Scheme 8).



Scheme 8

[0047] The starting compounds **38** were obtained by olefination of ketones **33** with diethyl cyanomethyl phosphonate **34** carried out in ether or DMF to provide nitriles **37**[42a]. Further reduction with DIBALH carried out in pentane or ether, gave known aldehydes **38a-c**[42b] (Scheme

8). Reduction of nitrile **37d**, performed in pentane or ether afforded aldehyde **38d**.

[0048] The stereoselective conversion of aldehydes **38** to (*E*)-α,β-unsaturated esters **39** was performed with triethyl phosphonoacetate **35**[43-44] in the presence of LiOH or BuLi. The stereoselective synthesis of (2*Z*)-4-cycloalkylidenebut-2-enoates **40** was achieved by Horner-Wadsworth-Emmons olefination performed on aldehydes **38** with ethyl (diphenylphosphono)acetate **36a** and ethyl (di-o-tolylphosphono) acetate **36b**, respectively, in the presence of Triton B in tetrahydrofuran.

[0049] Further basic hydrolysis of **40** under mild conditions afforded the corresponding (2*Z*)-4-cycloalkylidenebut-2-enoic acids **42** in excellent yields. The (*Z*)-acids **42** were converted to the corresponding sodium salts **44** by treatment with NaOH in MeOH.

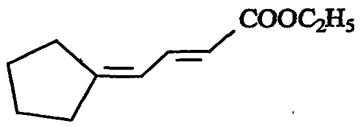
General Procedure for the Preparation of Ethyl (2E)-4-Cycloalkylidenebut-2-enoates (39a-d)

Method A: A suspension of $LiOH.H_2O$ (2.2 mmol) in anhyd THF (4 mL) was treated at room temperature with **35** (2.2 mmol) followed by aldehyde **38** (2 mmol) and stirred over 2.5 or 16 hours. The mixture was filtered through silica gel and washed with ether. The filtrate was concentrated under reduced pressure and the residue was purified by column (hexanes/ ether=100:1.5) to afford esters **39d** as a colourless liquid.

Method B: To a solution of triethyl phosphonoacetate **35** (30.06 mmol) in THF under argon at 0°C was added DMPU (7.58 ml) over 10 min and BuLi (21.8 ml) over 20 min and the stirring was continued for 20

minutes. The solution was then cooled to -78°C and a solution of aldehyde **38** (17.0 mmol) in THF was added dropwise over 1.5 h, stirred for 1h and the reaction mixture was allowed to warm to 0°C over 1.5 h. The reaction was quenched with sat. NH_4Cl solution, extracted with ethyl acetate, washed successively with H_2O and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield compounds **39**.

Ethyl (2*E*)-4-Cyclopentylidenebut-2-enoate (39a)



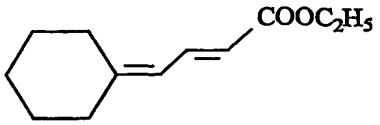
39a

Procedure A: Yield: 65%),

Procedure B: Yield: 50%.

^1H NMR (300 MHz, $CDCl_3$): 7.35 (dd, 1H), 6.0 (d, 1H), 5.62 (d, 1H), 4.11 (q, 2H), 2.41 (t, 2H), 2.31 (t, 2H), 1.68-1.57 (m, 4H), 1.24 (t, 3H);

Ethyl (2*E*)-4-Cyclohexylidenebut-2-enoate (39b)



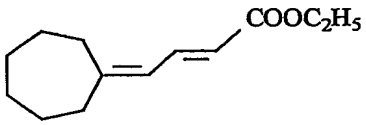
39b

Procedure A: Yield: 66%.

Procedure B: Yield: 71%.

^1H NMR (300 MHz, $CDCl_3$): 7.55 (dd, 1H), 5.89 (d, 1H), 5.74 (d, 1H), 4.15 (q, 2H), 2.41-2.29 (m, 2H), 2.21-2.11 (m, 2H), 1.58-1.54 (m, 6H), 1.24 (t, 3H).

Ethyl (2*E*)-4-Cycloheptylidenebut-2-enoate (39c):



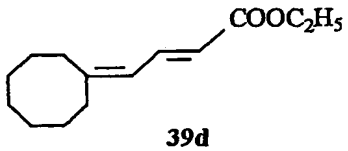
39c

Procedure A: Yield: 41%.

Procedure B: Yield: 64%.

^1H NMR (300 MHz, $CDCl_3$): 7.56 (dd, 1H), 5.96 (d, 1H), 5.79 (d, 1H), 4.18 (q, 2H), 2.51 (t, 2H), 2.33 (t, 2H), 1.69-1.61 (m, 3H), 1.50-1.41 (m, 5H), 1.27 (t, 3H).

Ethyl (2*E*)-4-Cyclooctylidenebut-2-enoate (39d)



39d

Procedure A: Yield: 58%.

Procedure B: Yield 70%)

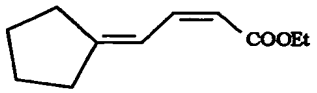
^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (dd, 1H), 5.96 (d, 1H), 5.69 (d, 1H), 4.16 (q, 2H), 2.41 (t, 2H), 2.25 (t, 2H), 1.69- 1.64 (m, 4H), 1.48-1.39 (m, 6H), 1.25 (t, 3H);

General procedure for the preparation of Ethyl (2*Z*)-4-Cycloalkylidenebut-2-enoates (40a-d)

To a solution of **36a/36b** (1 mmol) in THF (3 mL) at -78°C under argon was added dropwise Triton B (benzyltriethylammonium hydroxide 40% in MeOH) (0.54 mL, 1.35 mmol) over 15 minutes. After 30 minutes, a solution of aldehyde **38** (1.1 mmol) in THF (1 mL) was added dropwise for 20 minutes and the resulting mixture was gradually warmed to 0°C . The reaction was quenched with sat. NH_4Cl solution extracted with ethyl acetate and the combined organic layers were washed successively with H_2O and brine, dried ($MgSO_4$) and then concentrated in vacuo. The crude residue was purified on chromatotron (silica gel, hexanes followed by hexanes/Et_2O 100:1.5) to yield a mixture of (Z/E) products **40/39** determined by ^{1}H HMR analysis. Further separation of the

mixture afforded analytical samples of compounds **40** and **39**, respectively, as colourless liquids.

Ethyl (2*Z*)-4-Cyclopentylidenebut-2-enoate (40a)

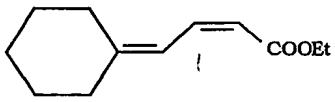


40a

Yield: From **36a** and **36b**: 47% and 56% respectively.

^{1}H NMR (300 MHz, $CDCl_3$): 7.21 (d, 1H), 6.65 (t, 1H), 5.44 (d, 1H), 4.09 (q, 2H), 2.36 (t, 4H), 1.67-1.56 (m, 4H), 1.2 (t, 3H).

Ethyl (2*Z*)-4-Cyclohexylidenebut-2-enoate (40b):

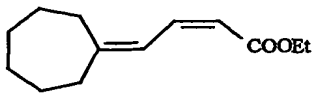


40b

Yield: From **36a** and **36b**: 61% and 67%, respectively.

^{1}H NMR (300 MHz, $CDCl_3$): 7.08 (d, 1H), 6.84 (t, 1H), 5.47 (d, 1H), 4.09 (q, 2H), 2.27 (br t, 2H), 2.18 (br t, 2H), 1.51-1.49 (m, 6H), 1.19 (t, 3H);

Ethyl (2*Z*)-4-Cycloheptylidenebut-2-enoate (40c)

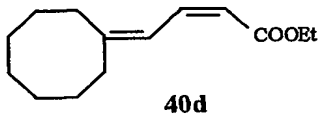


40c

Yield: From **36a** and **36b**: 45% and 76%, respectively.

^{1}H NMR (300 MHz, $CDCl_3$): 7.16 (d, 1H), 6.87 (t, 1H), 5.53 (d, 1H), 4.16 (q, 2H), 2.47 (t, 2H), 2.39 (t, 2H), 1.62 – 1.55 (m, 4H), 1.51-1.46 (m, 4H), 1.27 (t, 3H);

Ethyl (2*Z*)- 4-Cyclooctylidenebut-2-enoate (40d):



40d

Yield: From **36a** and **36b**: 48% and 82%, respectively.

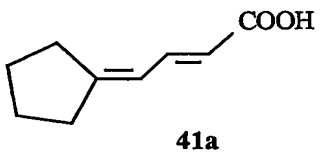
^{1}H NMR (300 MHz, $CDCl_3$): 7.21 (d, 1H), 6.87 (t, 1H), 5.51 (d, 1H), 4.14 (q, 2H), 2.38 (t, 2H), 2.32 (t, 2H), 1.70-1.66 (m, 4H), 1.49-1.44 (m, 6H), 1.25 (t, 3H);

General procedure for preparation of (2*E*)-4-Cycloalkylidenebut-2-enoic Acids (41a-d) and (2Z)-4-Cycloalkylidenebut-2-enoic Acids (42a-d)

A mixture of esters (*E*)-**39** or (*Z*)-**40** (0.44 mmol) and NaOH (1.2 g, 30

mmol) in H_2O/MeOH (7.8/3.9 mL) was gently refluxed for 45 min. After cooling the reaction mixture was diluted with brine (5 mL) and extracted with ether. The aqueous layer was acidified with 10% HCl, extracted with ethyl acetate), and the combined extracts washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Chromatotron chromatography (silica gel, hexanes/EtOAc 90:10) afforded pure acids (*E*)-**41** or (*Z*)-**42** respectively as a white solid.

(2*E*)-4-Cyclopentylidenebut-2-enoic Acid (41a)



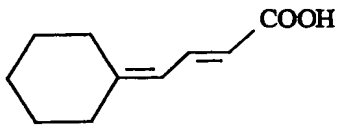
41a

Yield: 60%, mp 112-114°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.43 (dd, 1H), 6.12 (d, 1H), 5.67 (d, 1H), 2.48 (t, 2H), 2.39 (t, 2H), 1.79-1.63 (m, 4H).

IR (KBr): ν = 1679 cm^{-1}.

(2*E*)-4-Cyclohexylidenebut-2-enoic Acid (41b)



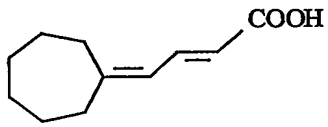
41b

Yield: 80%, mp 132-134°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.64 (dd, 1H), 5.99 (d, 1H), 5.75 (d, 1H), 2.39 (br s, 2H), 2.26 (br s, 2H), 1.61 (br d, 6H);

IR (KBr): ν = 1680 cm^{-1}.

(2E)-4-Cycloheptylidenebut-2-enoic Acid (41c)



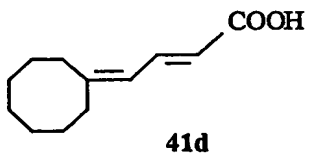
41c

Yield: 85%, mp 88-89°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.58 (dd, 1H), 6.02 (d, 1H), 5.74 (d, 1H), 2.53 (t, 2H), 2.32 (t, 2H), 1.75 (br d, 4H), 1.51 (br d, 4H).

IR (KBr): ν = 1680 cm^{-1}.

(2E)-4-Cyclooctylidenebut-2-enoic Acid (41d)



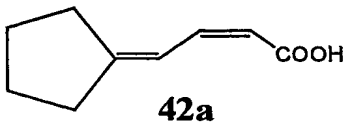
41d

Yield: 89%, mp 114-116°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (dd, 1H), 6.07 (d, 1H), 5.72 (d, 1H), 2.47 (t, 2H), 2.32 (t, 2H), 1.75 (br d, 4H), 1.51 (br d, 6H).

IR (KBr): ν = 1680 cm^{-1}.

(2Z)-4-Cyclopentylidenebut-2-enoic Acid (42a)



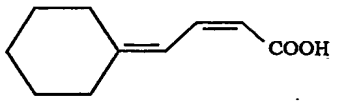
42a

Yield: 63%, mp 105-107°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (d, 1H), 6.79 (t, 1H), 5.49 (d, 1H), 2.47-2.39 (m, 4H), 1.79-1.62 (m, 4H).

IR (KBr): ν = 1684 cm^{-1}.

(2Z)-4-Cyclohexylidenebut-2-enoic Acid (42b)



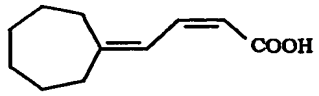
42b

Yield: 68%, mp 121-123°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.06 (d, 1H), 7.0 (d, 1H), 5.53 (d, 1H), 2.39 (br t, 2H), 2.34 (br t, 2H), 1.61 (br s, 6H).

IR (KBr): ν = 1680 cm^{-1}.

(2*Z*)-4-Cycloheptylidenebut-2-enoic Acid (42c)



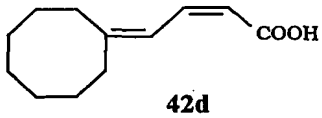
42c

Yield: 86%, mp 86-88°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, 1H), 6.94 (t, 1H), 5.53 (d, 1H), 2.51 (t, 2H), 2.39 (t, 2H), 1.65-1.64 (m, 4H), 1.54-1.52 (m, 4H).

IR (KBr): ν = 1684 cm^{-1}.

(2*Z*)-4-Cyclooctylidenebut-2-enoic Acid (42d)



42d

Yield: 64%, mp 110-112°C.

^{1}H NMR (300 MHz, $CDCl_3$): 7.16 (d, 1H), 6.97 (t, 1H), 5.53 (d, 1H), 2.45 (t, 2H), 2.33 (t, 2H), 1.79-1.68 (m, 4H, 1.58-1.46 (m, 6H).

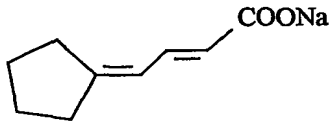
IR (KBr): ν = 1684 cm^{-1}.

General procedure for the preparation of Sodium (2*E*)-4-Cycloalkylidenebut-2-enoates (43a-d) and Sodium (2*Z*)-4-

Cycloalkylidenebut-2-enoates (44c,d)

To a solution of acid (*E*)-**41** or (*Z*)-**42** (2.4 mmol) in MeOH (10 mL) was added dropwise a solution of NaOH (2.18 mmol) in MeOH (20 mL) at 0°C under argon and the resulting mixture was warmed to room temperature overnight. The MeOH was concentrated under reduced pressure and the white solid formed was filtered, washed successfully with ether, and dried in vacuo to give pure sodium salt ((E)-**43**)/((Z)-**44**) as a white solid; mp > 300°C.

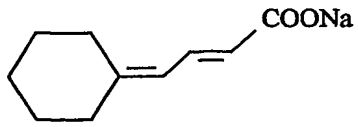
Sodium (2*E*)-4-Cyclopentylidenebut-2-enoate (43a)



43a

Yield: 87%, ^{1}H NMR (400 MHz, CD_3OD): 7.35 (dd, 1H), 6.03 (d, 1H), 5.73 (d, 1H), 2.46 (t, 2H), 2.36 (t, 2H), 1.73– 1.63 (m, 4H).

Sodium (2*E*)-4-Cyclohexylidenebut-2-enoate (43b)

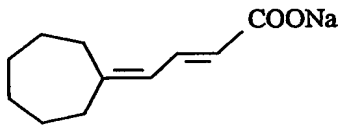


43b

Yield: 90%, ^{1}H NMR (400 MHz, CD_3OD): 7.40 (dd, 1H), 6.0 (d, 1H),

5.8 (d, 1H), 2.4 (br s, 2H), 2.2 (br s, 2H), 1.6 (br s, 6H).

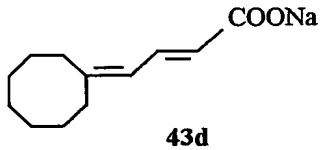
Sodium (2*E*)-4-Cycloheptylidenebut-2-enoate (43c)



43c

Yield: 77%, ^{1}H NMR (400 MHz, CD_3OD): 7.35 (dd, 1H), 5.93 (d, 1H), 5.78 (d, 1H), 2.51 (t, 2H), 2.33 (t, 2H), 1.73– 1.63 (m, 4H), 1.57– 1.52 (m, 4H).

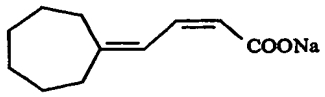
Sodium (2*E*)-4-Cyclooctylidenebut-2-enoate (43d)



43d

Yield: 76%, ^{1}H NMR (400 MHz, CD_3OD): 7.39 (dd, 1H), 5.97 (d, 1H), 5.77 (d, 1H), 2.45 (t, 2H), 2.28 (t, 2H), 1.78– 1.71 (m, 4H), 1.66– 1.51 (m, 6H).

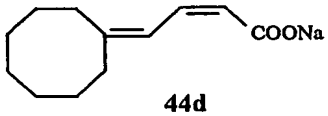
Sodium (2*Z*)-4-Cycloheptylidenebut-2-enoate (44c)



44c

Yield: 94%, ^{1}H NMR (300 MHz, CD_3OD): 6.97 (d, 1H), 6.51 (d, 1H), 5.65 (d, 1H), 2.44 (t, 2H), 2.34 (t, 2H), 1.63 – 1.59 (m, 4H), 1.56 - 1.51 (m, 4H).

Sodium (2*Z*)-4-Cyclooctylidenebut-2-enoate (44d)

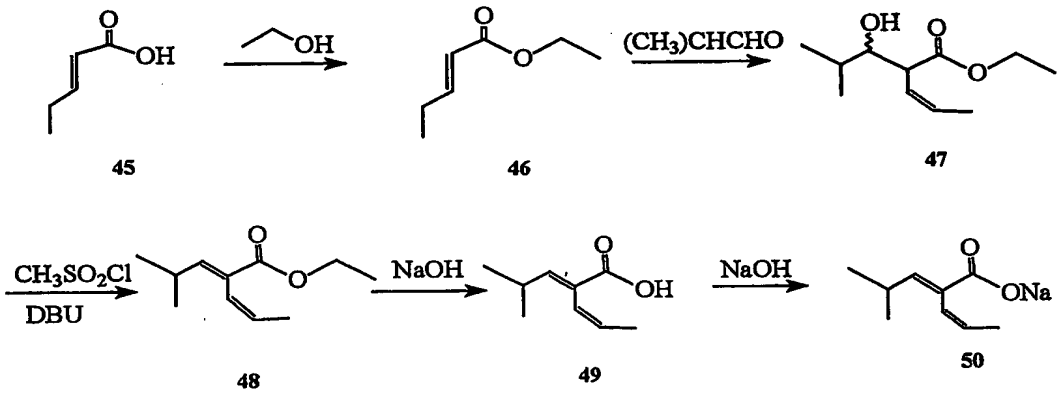


44d

Yield: 92%, ^{1}H NMR (300 MHz, $CDCl_3$): 7.04 (d, 1H), 6.56 (d, 1H), 5.48 (d, 1H), 2.39 (t, 2H), 2.29 (t, 2H), 1.71 (m, 4H), 1.51 (br s, 6H).

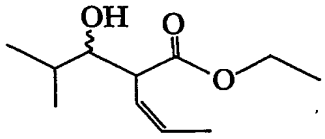
Example 3: Synthesis of Conjugated VPA Analogues

The synthesis of the target compound **50** is outlined in Scheme 9. The starting ester **46** was prepared from trans-2-pentenoic acid **45** by refluxing with an excess of ethyl alcohol in the presence of catalytic amounts of conc. H_2SO_4 in benzene. The ester **46** was allowed to react with isobutyraldehyde in the presence of LDA in tetrahydrofuran to afford alcohol **47**. Further mesylation of **47** with MsCl followed by elimination under basic conditions gave ester **48**. Upon basic hydrolysis of **48**, the acid **49** obtained was converted into its sodium salt **50** under the conditions described above for the preparation of the other sodium salts.



Scheme 9

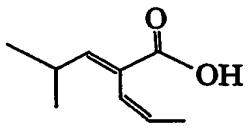
Preparation of ethyl (3Z)-2-(1-hydroxy-2-methylpropyl)pent-3-enoate (47)



47

8.18 g (bp 80-81°C/8 mmHg) of compound **47** were prepared according to the procedure described for compound **10** from 6.41g of ethyl (2*Z*)-pent-2-enoate and a solution of isobutyraldehyde (3.61 g) in tetrahydrofuran (7 ml) and a standard work-up procedure under acidic conditions.

Preparation of (2*E*)-4-methyl-2-[(1*Z*)-prop-1-enyl])pent-2-enoic acid (49).



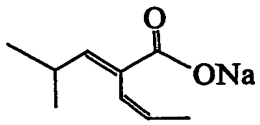
49

Step A: A mixture of 7.98 g of compound **47** and triethylamine (8.77 ml) in methylene chloride (66 ml) was treated dropwise with a solution of methanesulfonyl chloride (3.3 ml) in methylene chloride (4 ml) at 0°C. After 60 minutes the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (55 ml) and treated with a solution of DBU (6 ml). After refluxing for 2 hours the mixture was cooled, treated with H_2O (35 ml), extracted with ether, washed with brine, and dried over magnesium sulfate.

Step B: The ether **48** was evaporated under reduced pressure, and the crude residue was treated with 3N NaOH/H_2O (18.0 ml : 9.0 ml) and heated at 60°C for 48 hours. The mixture was then cooled, extracted with ether, and the aqueous phase was acidified with 10% HCl, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column on silica gel (hexane:ether= 9:1) to give 4.01 g of compound **49**.

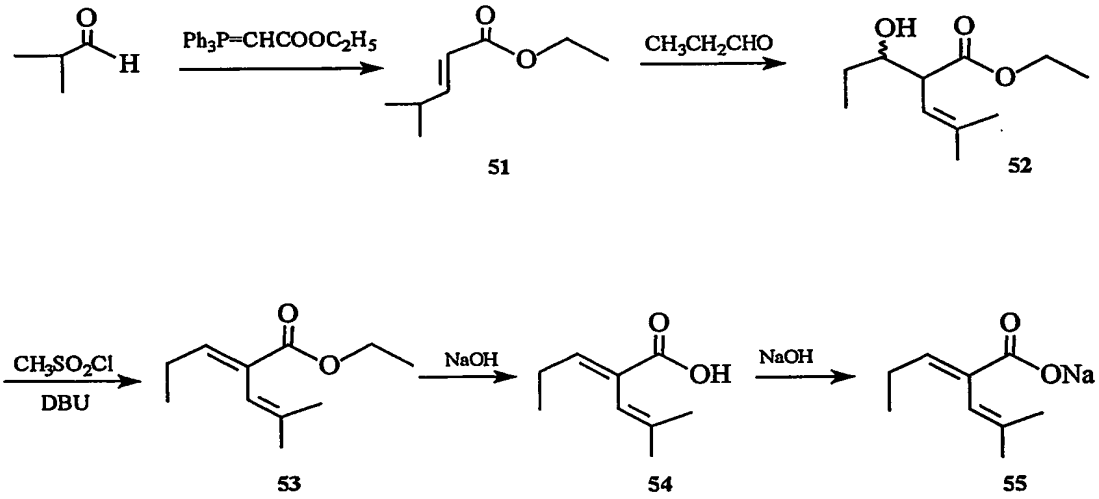
^{1}H NMR (300 MHz, $CDCl_3$): 11.95 (s, 1H), 6.73 (d, 1H), 5.91 (d, 1H), 5.77 (m, 1H), 2.54 (m, 1H), 1.55 (d, 3H), 0.97 (d, 6H).

Preparation of sodium (2*E*)-4-methyl-2-[(1*Z*)-prop-1-enyl])pent-2-enoate (50).



50

3.62 g of the compound **50** was prepared according to the procedure described above for compound **21** from 3.7 g of compound **49**.

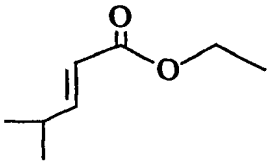


51 **52** **53** **54** **55**

Scheme 10

The synthesis of compound **55** is outlined in Scheme 10. The starting ester **51** was prepared from isobutyraldehyde under Wittig reaction's conditions. The ester **51** reacted with propanal under basic conditions to afford alcohol **52**. The sodium salt **55** was obtained under the conditions for the preparation of compound **50**.

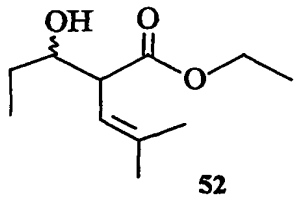
Preparation of ethyl (2*E*)-4-methylpent-2-enoate (51)



51

A mixture of (carbethoxymethylene)triphenylphosphorane (52.26 g) in methylene chloride (140 ml) was treated slowly with a solution of 2-methylpropionaldehyde (5.41 g) in methylene chloride (15 ml) and the reaction mixture was stirred at room temperature for 40 hours. The solvent was evaporated under reduced pressure and the residue obtained was washed with hexane and purified by column on silica gel (hexane:ethyl acetate= 10:1) to give 10.08 g of compound **51** as a colourless oil.

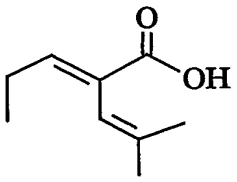
Preparation of ethyl 2-(1-hydroxypropyl)-4-methylpent-3-enoate (52)



52

2.04 g (bp 85-89°C/0.6 mmHg) of compound **52** was prepared according to the procedure described above for preparing product **47** from 2.53 g of ethyl (2*E*)-4-methylpent-2-enoate and a solution of 2-methylbutyraldehyde (1.53 g) in tetrahydrofuran (5 ml) and a standard work-up procedure under acidic conditions.

Preparation of (2*E*)-2-(2-methylprop-enyl)pent-2-enoic acid (54).

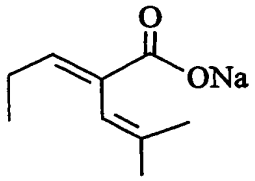


54

2.03 g of compound **54** was prepared according to the procedure described above for the preparation of product **49** from 3.62 g of compound **52**.

^{1}H NMR (300 MHz, $CDCl_3$): 11.89 (s, 1H), 6.86 (t, 1H), 5.69 (bs, 1H), 2.08 (m, 2H), 1.81 (s, 3H), 1.51 (s, 3H), 0.99 (t, 3H)

Preparation of sodium (2*E*)-2-(2-methylprop-enyl)pent-2-enoate (55)



55

750 mg of compound **55** was prepared according to the procedure described for the preparation of product **50** from 798 mg of product **54**.

Example 5: Pharmacological and Toxicological Testing

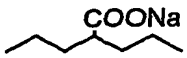
[0050] Anticonvulsant testing was conducted at the antiepileptic screening facility of the National Institute for Neurological Disorders and Stroke in Rockville, Maryland. Initial tests were done in mice (i.p.) followed by oral and i.p. administration to rats. Neurotoxicity was evaluated with the rotarod test. Maximal electroshock (MES) and subcutaneous methylene tetrazole (SCMET) or pentylene tetrazole (PTZ) were the most common tests performed. Typical procedures are described below.

[0051] **MES Assay.** Male CD1/CR mice weighing from 25-35 g are administrated test compounds 15 minutes prior to MES. Mice are challenged by pulsed electrical stimulation (50 mA, 0.4 s duration, pulse width 0.5 ms, 60 pulses/sec) via corneal electrodes to induce seizure. Mice are observed post-stimulation for the onset of tonic seizures, and considered to have a tonic seizure only if there is a prolonged extension (>90° from plane of body) of the hind legs. Mice that do not have a seizure, are considered to be protected. Ten mice are used in each group.

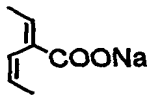
[0052] **SCMET (PTZ85) Assay.** Male CD1/CR mice weighing from 25-35 g are administrated test compounds (range of 5 doses) 15 minutes prior to PTZ. PTZ is administrated subcutaneously, just caudal to the cranium, at a dose of 85 mg/kg. Animals are then caged individually and observed for 15 minutes. The occurrence and latency to clonic and/or tonic convulsions are recorded. The mice are used once. Ten mice are used in each dose group. An animal is considered to be unprotected if it shows a 5s clonus with loss of balance. ED_{50} is determined from a graph of percentage protection vs log(dose) following the known method of Litchfield[18], where percentage protection refers to the percent of animals in each dose group which are protected against seizures.

[0053] **Rotorod Test.** Acute drug induced neurotoxicity is detected in mice using the standard rotorod test. An untreated mouse, when placed on a 6 rpm rotation rod, can maintain its equilibrium for a prolonged period of time. Drug induced neurological impairment is demonstrated by the mouse's inability to maintain equilibrium for one minute in each of three trials.

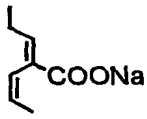
[0054] A number of VPA analogues and their sodium salts were tested for their efficacy as anticonvulsants and for their toxicity using the MES Assay and rotarod test. In particular, the following compounds (as shown in the structures below) were tested: 332059U (sodium salt of VPA), 325071 (known compound, tested for comparison), 325073A (metabolite of VPA), 332060U (4,4-difluoro-2-propylpentanoate, fluorinated analogue of VPA), 341031, and 341032U (conjugated (*E,Z*)-2,3'-diene VPA analogues). The results of the tests are summarized in Table 2.



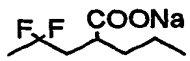
Add ID: 332059U (VPA)
Sodium 2-propylpentanoate



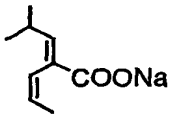
Add ID; 325071, (E,Z)-2,3'-diene
Sodium (2E,3Z)-2-ethylidenpent-3-enoate



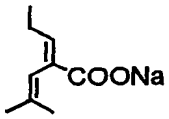
Add ID: 325073A, (E,Z)-2,3'-diene
Sodium (2E)-2-[(1Z)-prop-1-en-1-yl]pent-2-enoate



Add ID: 332060U, 4,4-difluoro-VPA, (7)
Sodium 4,4-difluoro-2-propylpentanoate



Add ID: 341031, (E,Z)-2,3'-diene, (50)
Sodium (2E)-4-methyl-2-[(1Z)-prop-1-en-1-yl]pent-2-enoate



Add ID: 341032U, (E,Z)-2,3'-diene, (55)
Sodium (2E)-2-(2-methylprop-1-en-1-yl)pent-2-enoate

Add ID	Test	Dose (mg/kg)	# Dths	0.25 h N/F	0.5 h N/F	1.0 h N/F	2.0 h N/F	4.0 h N/F	6.0 h N/F	8.0 h N/F	24h N/F	36h N/F
332059A	Sodium Valproate											
	MES	300		0/4	1/4	1/4	0/4	0/4	/	/	/	/
	MES	400		/	1/4	2/4	0/4	/	/	/	/	/
	TOX	300		0/4	0/4	0/4	0/4	0/4	/	/	/	/
	TOX	400		/	0/4	0/4	0/4	/	/	/	/	/
325071A	Sodium (2E, 3Z)-2-ethylidenpent-3-enoate											
	MES	80		0/4	0/4	0/4	0/4	0/4	/	/	/	/
	MES	200		0/4	1/4	0/4	1/4	0/4	/	/	/	/
	SCMET	80		0/4	0/4	1/4	0/4	0/4	/	/	/	/
	SCMET	200		2/4	0/4	0/4	1/4	1/4	/	/	/	/
	TOX	200		0/8	0/8	0/8	0/8	0/4	/	/	/	/
325073A	Sodium (2E)-2-[(1Z)-prop-1-en-1-yl]pent-2-enoate											
	MES	50		2/4	0/4	0/4	0/4	/	/	/	/	/
	SCMET	75		1/4	0/4	0/4	0/4	0/4	/	/	/	/
332060U	Sodium 4,4-difluoro-2-propylpentanoate											
	SCMET	100		1/4	1/4	0/4	0/4	0/4	/	/	/	/
	SCMET	200		1/4	1/4	/	/	/	/	/	/	/
	SCMET	360		3/4	0/4	2/4	1/4	0/4				
	TOX	100		0/4	0/4	0/4	0/4	0/4	/	/	/	/
	TOX	200		0/4	0/4	/	/	/	/	/	/	/
	TOX	360		0/4	0/4	0/4	0/4	0/4				
341031U	Sodium (2E)-4-methyl-2-[(1Z)-prop-1-en-1-yl]pent-2-enoate											
	MES	200		3/4	2/4	0/4	0/4	0/4	/	/	/	/
	TOX	200		0/4	0/4	0/4	0/4	0/4	/	/	/	/
341032U	Sodium (2E)-2-(2-methylprop-1-en-1-yl)pent-2-enoate											
	MES	200		4/4	3/4	1/4	0/4	0/4	/	/	/	/
	TOX	200		3/4	4/4	1/4	0/4	0/4	/	/	/	/

Table 2. Time to Peak Effect: Selected data obtained on Rats after Oral administration.

N/F = number of animals protected relative to number tested.

TOX: N/F = number of animals that failed the rotarod test to numbers tested.

MES = Maximal Electroshock.

SCMET = Subcutaneous Methylene Tetrazole

[0055] The data show that the difluoro analogue (332060U, (4,4-difluoro-2-propylpentanoate, fluorinated analogue of VPA)) is effective

at doses that do not demonstrate neurotoxicity. The diene analogues 341031U and 341032U are more potent than VPA, but demonstrate that the positioning of groups appears to be important to avoid overt neurotoxicity.

[0056] The compounds of interest were tested at an equivalent dose of 1800 micromoles on male cd1/cr mice using the PTZ85 Assay to induce clonic (repetitive seizures). Both the latency (time of seizure onset) and the number of animals protected increased with the size of the ring, or with increased lipophilicity.

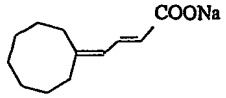
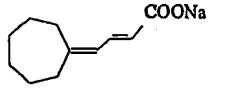
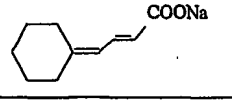
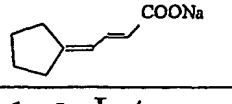
Compound	Seconds	SEM	Number of Mice Protected Against Clonic Seizures (Out of 10)
Control (Saline)	209	40	0
	855	45	9
	778	68	7
	661	86	4
	589	99	2

Table 3: Latency of Clonic Seizures at 1800 micromoles. SEM = Standard Error of the Mean.

[0057] The data indicate the importance of lipophilicity of the molecule to the observed potency, a property consistent with other VPA analogues[13].

Example 6: Pharmacological Studies of (E,Z)-2,3'-diene VPA

[0058] These compounds were investigated for anticonvulsant activity in mice[13] and rats (see results in Table 4) and found to be equivalent in potency to VPA.

COMPOUND	ED50, mg/kg	SLOPE
VPA	158 (144-187)	1.2 (1.1-1.3)
(E)-2-ENE VPA	185 (156-199)	1.2 (1.0-1.3)
(E,Z)-2,3'-DIENE VPA	168 (154-196)	1.2 (0.8-1.8)

Table 4: Mean effective doses against PTZ-induced seizures and the slopes of the log dose-response plots for each compound tested i.p. in male Sprague-Dawley rats (n=8).

[0059] The compound (*E,Z*)-2,3'-diene VPA has a very favorable anticonvulsant activity profile with respect to VPA (see Tables 2 and 4). Pharmacokinetic studies of (*E,Z*)-2,3'-diene VPA in the rat demonstrated rapid distribution to the brain, yet a significantly reduced affinity for the liver when compared to VPA (Figure 1, Table 5). The (*E*)-2-ene VPA metabolite had similar properties and at one time was being developed as a less hepatotoxic and nonteratogenic alternative to VPA[14]. The (*E,Z*)-2,3'-diene VPA appears to share the same properties. Comparative tissue distribution data for VPA and the unsaturated metabolites in rats are described in Table 5. As can be seen in Table 5, VPA has a great propensity to accumulate in the liver of rats. On the other hand, the unsaturated metabolites, (*E*)-2-ene VPA and (*E,Z*)-2,3'-diene VPA have markedly reduced affinities for liver.

	VPA	(*E*)-2-ene VPA	(*E*,*Z*)-2,3'-diene VPA
PLASMA	455 (68)	497 (38)	518
LIVER	854 (124)	384 (63)	241

Table 5: Area under the curve values ($AUC_{0\text{-}10h}$) in plasma and liver following the i.p. administration of VPA, (*E*)-2-ene VPA and (*E*,*Z*)-2,3'-diene VPA in equivalent doses(sodium salts) of 150 mg/kg to male Sprague-Dawley rats (n=8). $AUC_{0\text{-}10h}$ [ug.h/g or ml (SD)]

[0060] As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the scope thereof. Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

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